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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/027,671 | 02/23/1998 | ALAN K. SMITH | 4292-0048-55 | 3507 |

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| EXAMINER | |
|---|---|
| SAUNDERS, DAVID A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/027,671 | SMITH ET AL. | |
| | Examiner | Art Unit | |
| | David A. Saunders, PhD | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *18 November 2004 and 18 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *6,7,10-12,38-41,49-58 and 60-66* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-7,10-12,38-41,49-58 and 60-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/04 has been entered. The amendment has entered no new matter.

Claims 6-7,10-12,38-41,49-58 and 60-66 are pending. Claims 6-7,10-12,38-41,49-58 and 60-66 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The amendment has overcome previously stated issues as follows:

The rejection of claims 6-7,10-12,38-41and 49-69 under 35 USC 112, 2nd paragraph.

The rejection of claims 6-7,10-12,38-41and 49-69 under 35 USC 112, 1st paragraph.

The rejection of claim 69 under 35 USC 112, 1st paragraph.

The prior art rejection of claims 10-12,38-40 and 49 over Emerson et al. While the examiner does not know whether stromal cells should be considered "mature" or not (see new 112, 2nd infra), the rejection is withdrawn because it appears that "stromal cells" fall outside the scope of "hematopoietic cells". See spec. page 7, lines 12-20.

The prior art rejection of claims 10,12 and 38-40 over Caldwell et al. While the examiner does not know whether stromal cells should be considered "mature" or not (see new 112, 2nd infra), the rejection is withdrawn because it appears that "stromal cells" fall outside the scope of "hematopoietic cells". See spec. page 7, lines 12-20.

The following rejections of record are maintained or modified as follows:

Claims 10 and 38 are rejected under 35 U.S.C. 102(b) as being anticipated by Emerson et al (5,437,994 or 5,605,822 or 5,635,386 or 5,646,043, or 5,670,147 or 6,326,198).

In this stated rejection the examiner will consider aspects of Emerson et al not previously appreciated. Emerson et al show the culturing of cells at the instantly recited rate of medium replacement and instantly recited cell density. In some cases the culture medium was replaced at a rate of 50% daily, and in other cases at a rate of 100% (these culturing conditions are respectively designated as 7/wk and 3.5/wk). For example, see '043 at col.4, lines 37-44; col. 5, lines 42-58; col. 19, line 65-col. 20, line 54. While the teachings appear, on the surface, to relate to the culturing of haematopoietic stem cells and/or haematopoietic progenitor cells, rather than mature hematopoietic cells, one must consider the teachings to their full extent, and one must interpret the claims as they can be interpreted to their broadest reasonable extent. It is noted that Emerson et al teach that their rapidly exchanged cultures included a population of nonadherent cells; when the cell culture medium was replaced, these nonadherent cells were recovered from the old medium by centrifugation and returned to the culture along with the fresh medium; see a population of nonadherent cells included erythroid cells, late granulocytes, and macrophages; each of these cell types were produced in percentage amounts that varied with the week of culturing and with the combination of HGFs employed. See col. 26, line 60-col. 27, line 18. As far as the examiner can tell from the all embracing nature of applicant's disclosure, the erythroid cells, granulocytes/late granulocytes, and macrophages are properly deemed to be "mature" cells of haematopoeitic lineage.

It is noted that "comprising" in instant claim 38 permits the claim scope to include the culturing of haematopoietic stem cells an/or haematopoietic progenitor cells, along with "mature" haematopoeitic cells, such as erythroid cells, late granulocytes, and macrophages. Emerson et al are thus culturing the same type of "mature" cells as applicant.

Emerson et al characterize these mature cells of the nonadherent cell population by morphology (e.g. col. 22, lines 47-49) rather than by functional characteristics. However, given applicant's all embracing considerations of what constitutes "enhanced biological function", applicant's all embracing considerations of the types of cells to be cultured, and applicant's

disclosure that it is the medium exchange rate that results in the obtaining of cells with enhanced biological function, it is deemed that "enhanced biological function would have necessarily been a consequence of culturing the non adherent cell populations under the conditions taught by Emerson et al.

Regarding dependent claim 10, the mature cells of the nonadherent cell population would have been cultured for at least 2 days; because, on each day that the culture medium was replaced, when the cell culture medium was replaced, these nonadherent cells were recovered from the old medium by centrifugation and returned to the culture along with the fresh medium (col. 20, lines 42+).

The following grounds of objection/rejection are newly stated.

Applicant is advised that should claim 41 be found allowable, claim 52 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof, since there is no substantial difference in the terms "cytolytic activity" and "cytolysis". When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claims 6-7,10-12,38-41,49-58 and 60-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 38, "said conditions including replacement of a liquid culture medium is replaced" is confusing.

The claims are indefinite because the term "mature" is unclear. At spec. page 7, lines 3-4 applicant has defined "mature cells" as follows: 'As used herein, the term "mature cells" refers to cells which are terminally differentiated.' Subsequently in the specification, at page 8, lines 5-6, applicant refers to "the mature cells described above, especially T-cells". It is thus deemed that the term "mature human hematopoietic cells" in claim 38 would encompass "T-cells". However it is to be noted that T-cells can exist in various states of differentiation. For example, T-cells can

become activated, by cognate antigen or by a lectin, to undergo proliferation, to secrete cytokines, etc. For example, see Sitovsky (5,180,662) regarding activation of cytotoxic T-cells. Similarly, note Hazen et al (6,306,576) regarding activation of eosinophils. See Walz (5,401,651) regarding activation of neutrophils.

From the flip side, applicant has used the term "mature" to describe "mature myeloid cells" (page 8, line 3) as an example of "progenitor cells", which are not "terminally differentiated". One is thus uncertain as to just what "mature" means.

Claims 6-7,10-12,38-41,49-58 and 60-66 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Due to the confusion regarding what it means for a cell to be "mature" it is considered that applicant did not know what his invention was and did not adequately describe his invention. From the inconsistent usage of the term "mature" in the specification, one cannot envision what types of cells are or are not members of the genus of "mature cells".

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 38-39,49-51 and 53-55 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2,5-11 and 14-18 of U.S.

Patent No. 6,835,566. Although the conflicting claims are not identical, they are not patentably distinct from each other because the culturing of mature haematopoietic cells, as instantly claimed, would encompass the culturing of dendritic cells, as claimed in Pat. '566 (see spec. Page 7, lines 14-18 indicating that haematopoietic cells encompass dendritic cells). Also, the instantly recited culturing conditions, with respect to cell densities and culture fluid exchange rates, are encompassed by what is recited in claims 6 and 15 of Pat. '566. As far as the examiner can determine from the complex file histories of this application and Pat. '566, there was no restriction that resulted in applicant's filing of the claims issued in Pat.'566.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The Freedman et al reference (cited in the actions mailed 12/05/01, 10/16/02 and 12/23/03 and withdrawn in the action mailed 8/18/04) is again commented upon. The examiner notes that the action of 8/18/04 states that the 102 rejection over Freedman et al was withdrawn because "The taught medium exchange rates are in excess of what is recited in instant claim 38." The examiner therein based the exchange rate upon teachings referring to the perfusion rates of 60 ml/min or 300 ml/min (Freedman et al , page 148, coI.2). It is presently noted that a perfusion rate does not give a measure of the medium exchange rate, because not all of the volume of the perfusing medium crosses fiber membranes into the extra fiber space ("EFS", which contains the cells) in any single pass through of the perfusing medium through the fibers; rather the medium exchange rate would be based upon a more complex mathematical function, based on the perfusion rate and the rate of transport across the fiber membranes and the rates of diffusion within the ECS. This function is not disclosed by Freedman et al. In any event, there would be a continuous exchange of material between the circulating perfusion medium and the EFS. Because the perfusion medium continuously recirculates there would be a continuous depletion of nutrients (e.g. glucose) from the perfusing medium and a continuous build up of waste products (e.g. lactate) in the perfusion medium. Because of these factors, the medium supply for the perfusion medium circuit must be "replaced 3-8 times (mean 5.0)" (page 155, col. 1) over a time frame of 18.2 days (page 153, col. 2). It is thus taken that Freedman et al practiced a 100% exchange of medium (assuming a rapid exchange between the perfusing medium and the EFS) on the average of every 18.2 days/5, or 3.6 days. This is outside the range recited in claim 38.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is 571-272-0849. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Typed 9/30/05 DAS

David A Saunders

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